Cough and angiotensin II receptor antagonists: cause or confounding?

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Aims Cough is one of the most frequent side effects associated with angiotensin converting enzyme inhibitors (ACEIs) but is not thought to be associated with losartan, an angiotensin II receptor antagonist (ARA). This study compares reports of cough with losartan and three ACEIs used in general practice.

Methods Studies have been conducted for losartan, and three ACEIs enalapril, lisinopril and perindopril, using the technique of Prescription-Event Monitoring. Patients were identified using dispensed prescription data. Questionnaires were sent to patients' general practitioners 6 months after the date of first prescription. Cases of cough within the first 60 days of treatment with losartan resulting in withdrawal of the drug were followed up with additional questionnaires. Incidence rates for reports of cough were calculated. In order to reduce the impact of carry-over effects, rate ratios were calculated for first reports of cough between days 8 and 60 using losartan as the index drug.

Results The cohort for each drug exceeded 9000 patients. Age and sex distributions and indications for prescribing the four drugs were similar. Cough was the most frequent reason for discontinuation of losartan and the most frequently reported event in the first month of treatment with this drug. When reports of cough between days 1–7 were excluded, rates of cough were significantly higher for the three ACEIs when compared with losartan (rate ratios 1.5, 4.8 and 5.7, all $P<0.03$). 101 patients had discontinued losartan due to cough. 91% of these had previously been prescribed an ACEI and 86% had previously experienced ACEI cough.

Conclusions Carry-over accounted for the observed excess of reports of cough with losartan. Rates of cough between days 8 and 60 were significantly higher for the three ACEIs compared with losartan. Confounding factors associated with comparative observational cohort studies are discussed.

Keywords: cough, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, prescription-event monitoring, losartan

Introduction

Cough is one of the most frequent side effects associated with angiotensin converting enzyme inhibitors (ACEIs) but is not thought to be associated with selective angiotensin II receptor antagonists (ARAs) [1, 2]. Independent post-marketing surveillance studies have been conducted by means of Prescription-Event Monitoring (PEM) for three ACEIs; enalapril, lisinopril and perindopril, and the ARA, losartan, in general practice. Cough was the most frequent reason for discontinuation of losartan and the most frequently reported event in the first month of treatment. We compare the reporting of cough with the four drugs and discuss factors which affect event reporting in comparative observational cohort studies.

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Methods

The methodology of PEM has been described [3, 4]. Patients were identified from dispensed prescription data supplied in confidence by the Prescription Pricing Authority immediately after the UK launch of each drug (enalapril 1985, lisinopril 1988, perindopril 1990 and losartan 1995). All patients dispensed incident prescriptions for each drug in the immediate post-marketing period in England were identified. Questionnaires were posted to prescribing general practitioners 6 months following the first prescription for each patient. Identical methodology was employed for each study.

Questionnaires requested age, indication for treatment, starting and stopping dates of treatment, events during and after treatment and reasons for discontinuation.

Incidence rates were calculated for all events reported during treatment. The rates are expressed as number of first reports per 1000 patient-months of treatment. In order to reduce the impact of carry-over effects, incidence rates were calculated for reports of cough between days 8 and 60. Rate ratios were calculated using losartan as the index drug and adjusted for age and sex. Calculation of rates and adjusted rate ratios were performed using STATA statistical software [5].

Results

Comparison

The age and sex distributions of the four cohorts were comparable (Table 1). The principal indication for prescribing all four drugs was hypertension with a small proportion treated for cardiac failure. In order to reduce confounding by indication (cough as a symptom of cardiac failure) patients treated for cardiac failure, congestive cardiac failure, left ventricular failure, dyspnoea, oedema, pulmonary hypertension and pulmonary oedema were excluded from further analysis. Peak reporting of cough occurred at two-weekly intervals for all four drugs (Figure 1).

First reports of cough occurring during treatment between 8 and 60 days are shown in Table 2. Cough was most frequently reported among patients prescribed perindopril. Rate ratios adjusted for age and sex are shown in Table 3. First reports of cough between 8 and 60 days were significantly more frequent with all three ACEIs compared with losartan. Cough was reported more frequently among females than males for all four drugs but the difference was only statistically significant for lisinopril and perindopril (Table 4).

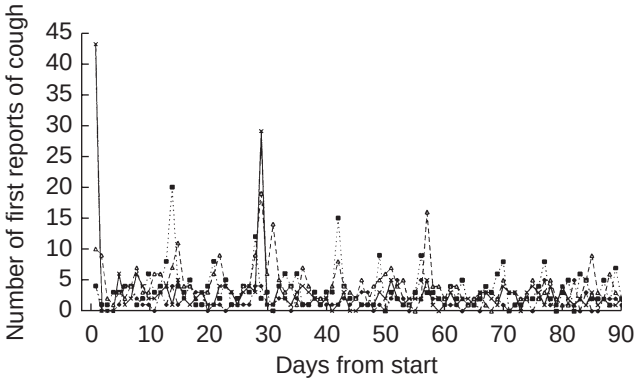

Figure 1 Reports of cough after start of therapy i—●— Enalapril $n=15361$, —■— Lisinopril $n=12438$, —△— Perindopril $n=9089$, —x— Losartan $n=14522$.

Cough and losartan

One thousand four hundred and eighteen (9.8%) of the original green form questionnaires for losartan reported previous ACEI cough as one of the indications for prescribing. Eight hundred and eighty-four (62.4%) of these were females and 527 (37.2%) were males. Only 94 (6.6%) of these patients experienced cough during treatment with losartan.

Two hundred and thirty-six patients experienced cough within 60 days of starting treatment with losartan and the drug was discontinued as a result in 101 (43%). These 101 cases were of particular interest. Comprehensive data were available for 54 of these cases and further questionnaires were sent to GPs for the remaining 47. After inclusion of follow-up data, 86 of the 94 cases for which data was available (91%) had previously been treated with ACEIs. Eighty-one (86% of the 94 cases with data) had previously experienced cough associated with ACEI therapy. The remaining 13 patients (14%) experienced cough for the first time after starting losartan. Data on

Table 1 Age and sex of patients.

	Enalapril	*Lisinopril*	*Perindopril*	*Losartan*
Cohorts	15 361	12 438	9089	14 522
Males				
Number (%)	7081 (46.1)	5469 (44.0)	4094 (45.0)	5834 (40.1)
Mean age (s.d.) (years)	59.4 (11.5)	58.7 (11.8)	59.8 (12.3)	61.1 (11.5)
Females				
Number (%)	7951 (51.8)	6712 (54.0)	4935 (54.3)	8617 (59.3)
Mean age (s.d.) (years)	62.8 (12.3)	62.8 (12.2)	63.5 (12.9)	65.1 (12.2)
Sex not specified	329 (2.1)	257 (2.1)	60 (0.7)	71 (0.5)
Age not specified	5671 (36.9)	928 (7.5)	768 (8.4)	1400 (9.6)
Indications (% specified)				
Hypertension	84.9	94.5	88.0	84.1
Cardiac failure	11.2	3.9	10.2	9.6

Table 2 Reports of cough between 8 and 60 days after start of treatment.

Drug	*Number of patients with cough*	*Patient-months of exposure*	*Rate per 1000 patient-months*	*95% confidence limits*
Enalapril	86	21 983	3.9	3.1–4.8
Lisinopril	270	18 749	14.4	12.7–16.2
Perindopril	210	12 751	16.4	14.3–18.8
Losartan	64	20 533	3.1	2.4–4.0

Table 3 Rate ratios (RR) for cough day 8 to 60: ACEIs compared with losartan.

Drug	*Crude RR*	*RR adjusted age and sex*	*95% confidence limits*	*(P value)*
Enalapril	1.3	1.5	1.1–2.2	(0.03)
Lisinopril	4.6	4.8	3.6–6.5	(<0.01)
Perindopril	5.3	5.7	4.2–7.6	(<0.01)

Table 4 Rate ratios (RR) for cough; females compared with males.

Drug	*Crude RR*	*RR adjusted for age*	*95% confidence limits*	*(P value)*
Enalapril	1.5	1.4	0.8–2.5	(0.17)
Lisinopril	1.6	1.6	1.2–2.2	(<0.01)
Perindopril	1.6	1.6	1.2–2.1	(<0.01)
Losartan	1.7	1.5	0.8–2.6	(0.19)

discontinuation of ACEI therapy were only available for 22 of the 47 patients sent further questionnaires (GPs were generally unsure about discontinuation dates). In 12 of these 22 cases patients had been switched directly (within 1 week) from ACEI to losartan but in nine cases ACEI therapy had been discontinued between 3 weeks and 2 years before (in one remaining case, treatment continued).

Smoking history was requested in 47 cases in which cough was the reason for stopping losartan. Seven patients were current smokers, eight ex-smokers and 15 never-smokers (GPs did not know for 17 patients). In terms of age, sex, concomitant medication and indication for treatment, patients who developed cough for the first time with losartan did not differ significantly from those who had a history of previous ACEI cough.

Discussion

This is the largest independent study to compare the incidence of cough with established ACEIs and the ARA losartan. The patients were those treated in 'every day' general practice. Predisposing factors for ACEI cough are thought to include age, sex (females), concomitant medication, duration of therapy, smoking status, pulmonary dysfunction and viral respiratory infection [1, 2]. The onset of ACEI cough is reported to occur in the first 8 weeks of treatment in 90% of cases and generally disappears within 1 week of withdrawal [1, 2]. It was therefore decided that reports of cough occurring after 7 days (to exclude possible 'carry-over' symptoms from immediately switching ACEI therapy) and within 60 days were most likely to include cases due to the study drugs. When analysis was undertaken for first reports during days 8 to 60, cough was significantly more frequent with all three ACEIs compared to losartan. These data, along with the follow-up data for patients who discontinued losartan due to cough suggest strongly that the majority of reports of cough with losartan were due to a 'carry-over' effect from previous ACEI therapy.

One thousand four hundred and eighteen (9.8%) of the losartan cohort had ACEI cough reported with the indication for prescribing. This underestimates the true prevalence because GPs were not specifically prompted to report ACEI intolerance. Only 6.6% of these patients went on to experience cough with losartan. The vast majority of patients (93.4%) with known ACEI cough therefore did not develop cough with losartan.

This study demonstrates a problem encountered in sequential observational cohort studies whereby drugs in a similar class are preferentially prescribed to patients who have experienced adverse events with earlier drugs, so-called 'channelling'. It can often be difficult to quantify the extent to which channelling affects studies but in this study we know that 86% of patients who discontinued losartan due to cough for whom questionnaires had been completed had previously experienced cough with ACEIs. *De novo* cough did occur with losartan (13 of the cases of cough which resulted in discontinuation of therapy) but reports were uncommon. 43% of patients who reported cough during treatment with losartan discontinued the drug for this reason. If cough in these patients was due to a 'carry-over' effect from previous ACEI therapy symptoms may have eventually resolved with continued use of losartan. In such cases rechallenge with the drug after a washout period should be of value.

The rate of reporting of cough with enalapril was much lower than that for lisinopril and perindopril but there is no specific reason why the incidence of cough should increase with each successive ACEI. Wide recognition of cough as a side-effect of ACEIs in the late 1980s may have affected the reporting rate in the two studies (lisinopril and perindopril) carried out after this time [6]. This may be an example of publicity bias affecting reporting rate. Patients may be preferentially prescribed an older ACEI first and then transferred to a newer agent if they develop cough. This may also account for increased rates of cough with the newer agents.

Peak reporting of cough occurred at two-weekly and monthly intervals for all four drugs which reflects the dates of entry in medical records by GPs (date of patient review) rather than the actual dates of onset of symptoms. Such an effect may be even more marked with computerised general practice databases which have an automatic 'default date' (date of entry) for ease of use when entering consultation details. Peak reporting of symptoms are likely to affect results of time-phase analysis for observation periods of less than 1 month. We compared reports of cough between 8 and 60 days with all four drugs. Any reporting bias would have affected all drugs similarly and should not have influenced the comparison.

This is a large independently conducted study comparing the incidence of cough with three established ACEIs and the ARA losartan, used in general practice. The majority of reports of cough associated with losartan can be explained as a result of a 'carry-over' effect. After minimising 'carry-over' by excluding reports of cough in the first seven days of treatment, the incidence of cough with losartan was significantly lower than with the ACEIs during the first 60 days of treatment. The majority of patients who were intolerant of ACEIs due to cough did not go on to report cough with losartan. The importance of 'carry-over' and other confounding factors associated with sequential observational cohort studies are discussed.

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